

LITE DEPALMA GREENBERG, LLC

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*Attorneys for Plaintiffs Teva Pharmaceuticals USA, Inc.,
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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

TEVA PHARMACEUTICALS USA, INC.,	:	
TEVA PHARMACEUTICAL INDUSTRIES	:	Civil Action No.:
LTD., TEVA NEUROSCIENCE, INC., and	:	
YEDA RESEARCH AND DEVELOPMENT	:	
CO., LTD.,	:	
	:	
<i>Plaintiffs,</i>	:	
	:	<u>COMPLAINT</u>
v.	:	
DR. REDDY'S LABORATORIES, LTD.,	:	
and DR. REDDY'S LABORATORIES, INC.,	:	
	:	
<i>Defendants.</i>	:	

Plaintiffs Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. (collectively “Plaintiffs” or “Teva”) bring this action for patent infringement and declaratory judgment against defendants Dr. Reddy’s Laboratories, Ltd., and Dr. Reddy’s Laboratories, Inc. (collectively “DRL”).

NATURE OF THE ACTION

1. This is an action by Teva for infringement of United States Patent No. 5,800,808 (“the ’808 patent”). This action arises out of the filing of an Abbreviated New Drug Application (“ANDA”) by DRL seeking approval by the United States Food and Drug Administration (“FDA”) to sell generic versions of COPAXONE® 20 mg/mL, 1 mL syringes, injection

(“COPAXONE®”), Teva’s innovative treatment for patients with relapsing-remitting forms of multiple sclerosis, prior to the expiration of the ’808 patent.

THE PARTIES

Teva

2. Teva Pharmaceuticals USA, Inc. (“Teva USA”) is a Delaware corporation with its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454-1090.
3. Teva Pharmaceutical Industries Ltd. (“Teva Ltd.”) is an Israeli company with its principal place of business at 5 Basel Street, P.O. Box 3190, Petah Tikva, 49131, Israel.
4. Teva Neuroscience, Inc. (“Teva Neuroscience”) is a Delaware corporation with its principal place of business at 901 E. 104th Street, Suite 900, Kansas City, Missouri 64131.
5. Yeda Research and Development Co. Ltd. (“Yeda”) is an Israeli company with its principal place of business at P.O. Box 95, Rehovot, 76100, Israel.

DRL

6. Upon information and belief, Dr. Reddy’s Laboratories, Inc. (“DRL Inc.”) is a corporation organized and existing under the laws of New Jersey with its principal place of business at 107 College Road East, Princeton, NJ 08540.
7. Upon information and belief, Defendant Dr. Reddy’s Laboratories, Ltd. (“DRL Ltd.”) is a corporation organized and existing under the laws of India with its principal place of business at 8-2-337, Road No. 3, Banjara Hills, Hyderabad, Telangana, India 500 034.
8. On information and belief, Defendant DRL Inc. is a wholly-owned subsidiary of DRL Ltd., and is controlled by DRL Ltd.

JURISDICTION AND VENUE

9. This action for patent infringement arises under 35 U.S.C. § 271.

10. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202.

11. Venue is proper in this Judicial District under 28 U.S.C. §§ 1391 and 1400(b).

12. Teva sells COPAXONE® throughout the United States, including within the State of New Jersey.

Dr. Reddy's Laboratories, Inc.

13. This Court has personal jurisdiction over Defendant DRL Inc.

14. Defendant DRL Inc. is a company incorporated in the state of New Jersey according to records filed with the State of New Jersey Division of Revenue and Enterprise Services.

15. Upon information and belief, DRL Inc. is a company with its principal place of business in the state of New Jersey.

16. Upon information and belief, Defendant DRL Inc. markets, distributes, and/or sells generic drugs within the State of New Jersey and throughout the United States.

17. Upon information and belief, Defendant DRL Inc. has engaged in and maintained systematic and continuous business contacts within the state of New Jersey, and has purposefully availed itself of the benefits and protections of the laws of New Jersey rendering it at home in New Jersey.

18. Upon information and belief, Defendant DRL Inc. routinely files ANDAs in the United States, including in New Jersey, and markets dozens of generic pharmaceutical products, including, *inter alia*, fenofibrate, amlodipine, levalbuterol, and risperidone.

19. Upon information and belief, Defendant DRL Inc. has agreements with pharmaceutical retailers, wholesalers or distributors providing for the distribution of its products

in the State of New Jersey, including, *inter alia*, fenofibrate, amlodipine, levalbuterol, and risperidone.

20. Upon information and belief, Defendant DRL Inc. has engaged in and maintained systematic and continuous business contacts within the State of New Jersey as well as purposefully availed itself of the protections of New Jersey law, and therefore has sufficient minimum contacts with the State of New Jersey.

21. Upon information and belief, Defendant DRL Inc. has applied for FDA approval to market and sell a generic version of COPAXONE® 20 mg/mL, 1 mL syringes, throughout the United States, including in New Jersey.

22. Upon information and belief, Defendant DRL Inc. will market, sell, and offer for sale its proposed generic version of COPAXONE® 20 mg/mL, 1 mL syringes, in the State of New Jersey following FDA approval of that product.

23. Upon information and belief, as a result of DRL's marketing, selling, or offering for sale of its generic version of COPAXONE® 20 mg/mL, 1 mL syringes, in the State of New Jersey, Teva will lose sales of COPAXONE® and be injured in the State of New Jersey.

24. Upon information and belief, Defendant DRL Inc. will commit, aid, abet, contribute to, and/or participate in the commission of the tortious action of patent infringement that will lead to foreseeable harm and injury to Teva, which manufactures COPAXONE® for sale and use throughout the United States, including the State of New Jersey.

25. Upon information and belief, Defendant DRL Inc. has admitted to jurisdiction in this Court. *See Dr. Reddy's Labs, Inc. v. Thompson*, CA. No. 02-cv-00452-WGB (D.N.J.).

26. Upon information and belief, this Court also has personal jurisdiction over Defendant DRL Inc. because it previously has been sued in this district without challenging this

Court's assertion of personal jurisdiction over it, and availed itself of this forum by asserting counterclaims for the purpose of litigating a patent infringement dispute. *See, e.g., AstraZeneca AB v. Dr. Reddy's Labs, Inc.*, CA. No. 11-cv-2317-JAP (D.N.J.).

27. Upon information and belief, this Court has personal jurisdiction over Defendant DRL Inc. for the reasons stated herein, including, *inter alia*, Defendant DRL Inc.'s activities in the forum, activities directed at the forum, and significant contacts with the forum, all of which render Defendant DRL Inc. at home in the forum.

Dr. Reddy's Laboratories, Ltd.

28. Upon information and belief, this Court has personal jurisdiction over Defendant DRL Ltd.

29. Upon information and belief, Defendant DRL Ltd. (through its subsidiary, Defendant DRL Inc.) markets, distributes and/or sells generic drugs within the State of New Jersey and throughout the United States.

30. Upon information and belief, Defendant DRL Ltd. has engaged in and maintained systematic and continuous business contacts within the State of New Jersey as well as purposefully availed itself of the protections of New Jersey law and therefore has sufficient minimum contacts with the State of New Jersey.

31. Upon information and belief, Defendant DRL Ltd. is partnering with Defendant DRL Inc. to attempt to bring a generic version of COPAXONE® glatiramer acetate injection, 20 mg/mL, 1 mL syringes, to market in the United States. *See Dr. Reddy's Laboratories Limited Q1 FY 2014 Earnings Call Transcript.* <http://www.drreddys.com/investors/pdf/Q1FY14-Earnings-Call-Transcript.pdf>.

32. Upon information and belief, Defendant DRL Ltd. collaborated and/or acted in concert with Defendant DRL Inc. to apply for FDA approval to market and sell a generic version

of COPAXONE® 20 mg/mL, 1 mL syringes, throughout the United States, including in New Jersey.

33. Upon information and belief, as a result of DRL Ltd.'s conduct, DRL will market, sell, and offer for sale its generic version of COPAXONE® 20 mg/mL, 1 mL syringes, in the State of New Jersey following FDA approval of that product.

34. Upon information and belief, Defendant DRL Ltd. will commit, aid, abet, contribute to and/or participate in the commission of the tortious action of patent infringement that will lead to foreseeable harm and injury to Teva, which manufactures COPAXONE® for sale and use throughout the United States, including the State of New Jersey.

35. Upon information and belief, as a result of DRL's marketing, selling, or offering for sale of its generic version of COPAXONE® 20 mg/mL, 1 mL syringes, in the State of New Jersey, Teva will lose sales of COPAXONE® and be injured in the State of New Jersey.

36. Upon information and belief, this Court also has personal jurisdiction over Defendant DRL Ltd. because it previously has been sued in this district without challenging this Court's assertion of personal jurisdiction over it, and availed itself of this forum by asserting counterclaims for the purpose of litigating a patent infringement dispute. *See, e.g., Astrazeneca AB v. Dr. Reddy's Labs, Inc.*, CA. No. 11-cv-2317-JAP (D.N.J.).

37. This Court also has personal jurisdiction over DRL Ltd. under Federal Rule of Civil Procedure 4(k)(2).

38. Upon information and belief, this Court has personal jurisdiction over Defendant DRL Ltd. for the reasons stated herein, including, *inter alia*, Defendant DRL Ltd.'s activities in the forum, activities directed at the forum, and significant contacts with the forum.

39. Upon information and belief, following any FDA approval of DRL's ANDA,

Defendants DRL Inc. and DRL Ltd. will work in concert with one another to make, use, offer to sell, and sell a generic version of COPAXONE® 20 mg/mL, 1 mL syringes, throughout the United States, including in New Jersey.

40. Upon information and belief, DRL Ltd. will manufacture DRL's proposed generic version of COPAXONE® 20 mg/mL, 1 mL syringes, on behalf of DRL Inc., and DRL Inc. will act as the agent of DRL Ltd. for sale of that product in the United States, including New Jersey.

BACKGROUND

The '808 Patent

41. The '808 patent, entitled "Copolymer-1 Improvements on Compositions of Copolymers," was duly and legally issued to Yeda by the United States Patent and Trademark Office on September 1, 1998, and expires on September 1, 2015. The '808 Patent has one claim.

42. Eliezer Konfino, Michael Sela, Dvora Teitelbaum, and Ruth Arnon are named inventors of the '808 patent.

43. Since the issuance of the '808 patent, Yeda has been and remains the sole owner by assignment of all rights, title and interest in the '808 patent.

44. Teva Ltd. is the exclusive licensee of the '808 patent.

45. A true and correct copy of the '808 patent is attached as Exhibit A.

Prior Litigation Involving the '808 Patent

46. Plaintiffs have previously asserted the '808 patent against generic manufacturers. Specifically, in 2008 and 2009, Plaintiffs brought patent infringement actions in the Southern District of New York against defendants Sandoz Inc. and Momenta Pharmaceuticals Inc. (together, "Sandoz"), and Mylan Pharmaceuticals Inc., Mylan Inc., and Natco Pharma Ltd. (together, "Mylan"), in response to Sandoz and Mylan's filings of ANDAs with paragraph IV

certifications seeking FDA approval of generic versions of Copaxone®. *See* C.A. No. 08-cv-7611 (S.D.N.Y.); C.A. No. 09-cv-8824 (S.D.N.Y.).

47. In June 2012, the Southern District of New York issued a Final Judgment in the above referenced cases, holding, *inter alia*, the '808 patent infringed by Sandoz and Mylan's ANDA products and rejecting Sandoz and Mylan's invalidity and unenforceability arguments. Sandoz and Mylan appealed to the Federal Circuit.

48. On July 24, 2013, the Federal Circuit issued an opinion affirming the district court's rulings on infringement, obviousness, and enablement, but reversing the district court's ruling on indefiniteness as to the '808 patent. The Federal Circuit held the term "molecular weight," as recited in claim 1 of the '808 patent, indefinite under 35 U.S.C. § 112.

49. On January 16, 2014, Teva petitioned the Supreme Court of the United States for a writ of *certiorari* presenting the question "whether a district court's factual finding in support of its construction of a patent claim term may be reviewed *de novo*, as the Federal Circuit requires (and as the panel explicitly did in this case), or only for clear error, as Rule 52(a) requires." Teva also sought reversal of the Federal Circuit's decision invalidating the '808 patent on that basis. The Supreme Court granted Teva's petition for writ of *certiorari* on March 31, 2014 and heard oral argument on October 15, 2014.

50. On January 20, 2015, the Supreme Court ordered the vacatur of the judgment of the Federal Circuit that the '808 patent is invalid.

Teva's COPAXONE® Product

51. Teva USA is the holder of New Drug Application ("NDA") number 02-0622, approved by the United States Food and Drug Administration ("FDA") for the use of glatiramer acetate, marketed as COPAXONE®, for the treatment of patients with relapsing forms of

multiple sclerosis.

52. Teva's innovative COPAXONE® product is manufactured by Teva Pharmaceutical Industries Ltd., and marketed and sold in the United States by Teva Neuroscience, Inc.

53. The active drug ingredient in COPAXONE® is glatiramer acetate. Glatiramer acetate is a complex mixture of polypeptide chains made from four amino acid building blocks. The individual polypeptide chains in glatiramer acetate vary in length and the sequence in which the amino acids are connected together, and thus in their molecular weight, which is expressed in the unit kilodaltons. The label for COPAXONE® requires the product to have an average molecular weight of 5 to 9 kilodaltons, where "average molecular weight" refers to a peak average molecular weight calculated by size exclusion chromatography.

54. The invention claimed in the '808 patent reflects, in part, the discovery that mixtures of relatively low molecular weight chains of glatiramer acetate provide therapeutic effectiveness against multiple sclerosis while lowering toxicity.

55. Teva practices claim 1 of the '808 patent in manufacturing COPAXONE®. In manufacturing COPAXONE®, Teva reacts protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1; treats the trifluoroacetyl copolymer-1 with aqueous piperidine to form copolymer-1; and purifies the copolymer-1. Through the process embodied in the '808 patent, Teva's COPAXONE® glatiramer acetate product has an average molecular weight of about 5 to 9 kilodaltons, where "average molecular weight" refers to a peak average molecular weight determined by size exclusion chromatography.

The DRL ANDA

56. Upon information and belief, DRL filed an ANDA under 21 U.S.C. § 355(j)

seeking FDA approval to manufacture, use, offer for sale, sell in and import into the United States, including New Jersey, glatiramer acetate injection, 20 mg/mL, 1 mL syringes, purported to be generic to Teva's COPAXONE® ("DRL's glatiramer acetate product"), prior to the expiration of the '808 patent.

57. Upon information and belief, DRL Inc., and DRL Ltd. submitted, collaborated, and/or acted in concert in the preparation or submission of this ANDA.

58. In order to be approved by the FDA, the drug product described in an ANDA must be equivalent to the innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use.

59. In order to be approved by the FDA, the active ingredient in an ANDA product must be "the same as" the innovator's active ingredient. Thus, generic applicants must scientifically demonstrate that the active ingredient in their product is "the same as" the active ingredient in the innovator's product.

60. Given its complexity, COPAXONE® cannot be fully characterized. Moreover, the method of action of COPAXONE® has not been fully elucidated. Thus, while COPAXONE® has been demonstrated to be a safe and effective treatment for relapsing-remitting multiple sclerosis, the attributes of the product responsible for this safe and efficacious treatment have not been fully identified.

61. It is believed that the method of manufacturing COPAXONE® and the average molecular weight of COPAXONE® play a role in the action and effectiveness of Teva's COPAXONE® product.

62. On information and belief, DRL must produce their generic glatiramer acetate product using a process that infringes claim 1 of the '808 patent in order for the product to be the

same as Teva's COPAXONE®, as required by the FDA for any approval of DRL's product.

**COUNT I FOR DECLARATORY JUDGMENT OF
INFRINGEMENT OF U.S. PATENT NO. 5,800,808 BY DEFENDANTS**

63. The allegations of the proceeding paragraphs 1-62 are realleged and incorporated herein by reference.

64. Upon information and belief, Defendants plan to begin manufacturing, marketing, selling, offering to sell and/or importing DRL's generic glatiramer acetate product soon after FDA approval. *See* Dr. Reddy's Laboratories Limited Q1 FY 2014 Earnings Call Transcript. <http://www.drreddys.com/investors/pdf/Q1FY14-Earnings-Call-Transcript.pdf>.

65. Such conduct will constitute direct infringement of the '808 patent under 35 U.S.C. § 271(a), inducement of infringement of the '808 patent under 35 U.S.C. § 271(b), contributory infringement under 35 U.S.C. § 271(c), and infringement of the '808 patent under 35 U.S.C. § 271(g).

66. Defendants' infringing patent activity complained of herein is imminent and will begin following FDA approval of the DRL ANDA.

67. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Teva and DRL as to liability for the infringement of the '808 patent. DRL's actions have created in Teva a reasonable apprehension of irreparable harm and loss resulting from DRL's threatened imminent actions.

68. Upon information and belief, DRL will knowingly and willfully infringe the '808 patent.

69. Teva will be irreparably harmed if DRL is not enjoined from infringing the '808 patent.

PRAYER FOR RELIEF

WHEREFORE, Teva respectfully requests the following relief:

- (a) a judgment that the '808 patent is valid and enforceable;
- (b) a judgment that the making, using, offering to sell, selling, marketing, distributing, or importing of DRL's glatiramer acetate product prior to the expiration of the '808 patent will infringe, actively induce infringement, and/or contribute to the infringement of one or more claims of the '808 patent;
- (c) an Order pursuant to 35 U.S.C. § 283 preliminarily and permanently enjoining Defendants and all persons acting in concert with Defendants from commercially manufacturing, using, offering for sale, selling, marketing, distributing, or importing DRL's glatiramer acetate product, or any product or compound the use of which infringes the '808 patent, or inducing or contributing to the infringement of the '808 patent until after the expiration of the '808 patent;
- (d) an award of Teva's damages or other monetary relief to compensate Teva if Defendants engage in the commercial manufacture, use, offer to sell, sale, or marketing or distribution in, or importation into the United States of DRL's glatiramer acetate product, or any product or compound the use of which infringes the '808 patent, or the inducement or contribution of the foregoing, prior to the expiration of the '808 patent in accordance with 35 U.S.C. § 284;
- (e) a judgment that this is an exceptional case and an award to Teva of its attorneys' fees under 35 U.S.C. § 285;
- (f) an award of Teva's reasonable costs and expenses in this action; and
- (g) an award of any further and additional relief to Teva as this Court deems just and proper.

Dated: January 22, 2015

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CERTIFICATION PURSUANT TO LOCAL CIVIL RULE 11.2

Plaintiffs Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. and Yeda Research and Development Co., Ltd., by its attorneys, hereby certifies that the matter in controversy in this action is related to the following action before the following actions;

- Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. v. Sandoz, Inc., Sandoz International GMBH, Novartis AG, and Momenta Pharmaceuticals, Inc., Civil Action No. 08-CV-7611-WHP-AJP [Rel. Civ. Act. No. 1 :09-cv-08824-WHP; 1:09-cv-10112-KBF; and 2:12-cv-02556-WHP]; joined with Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. v. Mylan Pharmaceuticals Inc., Mylan Inc. and Natco Pharma Ltd., Civil Action No. 09-CV-8824-WHP-AJP [Rel. Civ. Act. No. 1:08-cv-7611-WHP-AJP] (S.D.N.Y.)
- Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc., and Yeda Research and Development Co. Ltd. v. Synthon Pharmaceuticals, Inc., Synthon Holding B.V., Synthon B.V., and Synthon Holding s.r.o, Civil Action No. 12-cv-02556-WHP (S.D.N.Y.)

I hereby certify that the following statements made by me are true. I am aware that if any of the foregoing statements made by me are willfully false, I am subject to punishment.

Dated: January 22, 2015

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EXHIBIT A



US005800808A

United States Patent [19]

Konfino et al.

[11] Patent Number: **5,800,808**
 [45] Date of Patent: **Sep. 1, 1998**

[54] COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

[75] Inventors: Eliezer Konfino, Ramat Gan; Michael Sela, Rehovot; Dvora Teitelbaum, Rehovot; Ruth Arnon, Rehovot, all of Israel

[73] Assignee: Veda Research and Development Co., Ltd., Rehovot, Israel

[21] Appl. No.: 447,146

[22] Filed: May 22, 1995

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 344,248, Nov. 23, 1994, abandoned, which is a continuation of Ser. No. 248,037, May 24, 1994, abandoned.

[51] Int. Cl.⁶ **A61K 27/00**

[52] U.S. Cl. **424/78.08; 424/78.26; 424/78.29; 514/561; 525/420; 525/434; 525/435; 528/328**

[58] Field of Search **424/78.29, 78.08, 424/78.26; 514/561; 525/420, 434, 435; 528/328**

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(List continued on next page.)

Primary Examiner—Frederick Krass
Attorney, Agent, or Firm—Kenyon & Kenyon

[57] ABSTRACT

The present invention relates to an improved composition of copolymer-1 comprising copolymer-1 substantially free of species having a molecular weight of over 40 kilodaltons.

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Sheet 1 of 2

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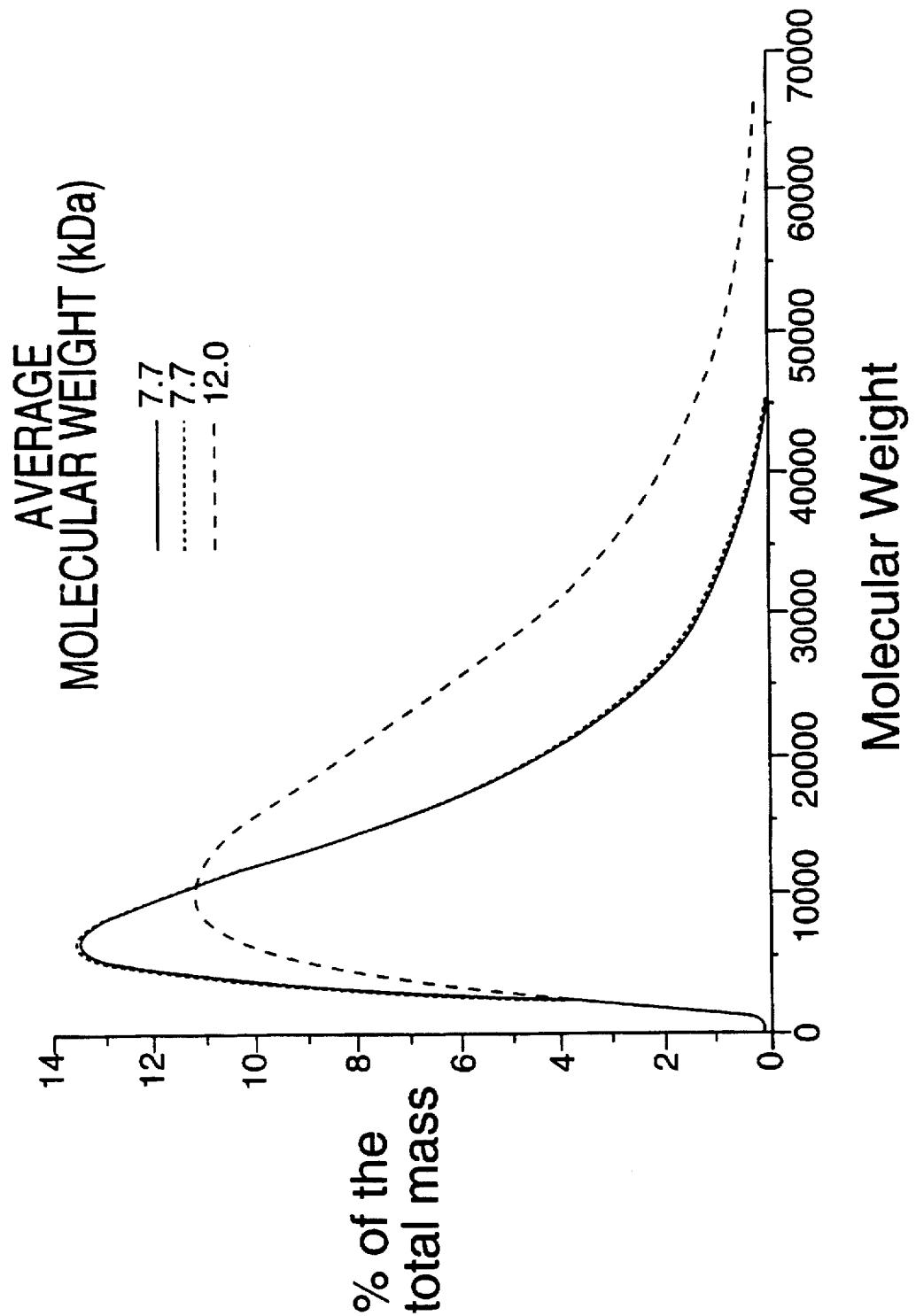


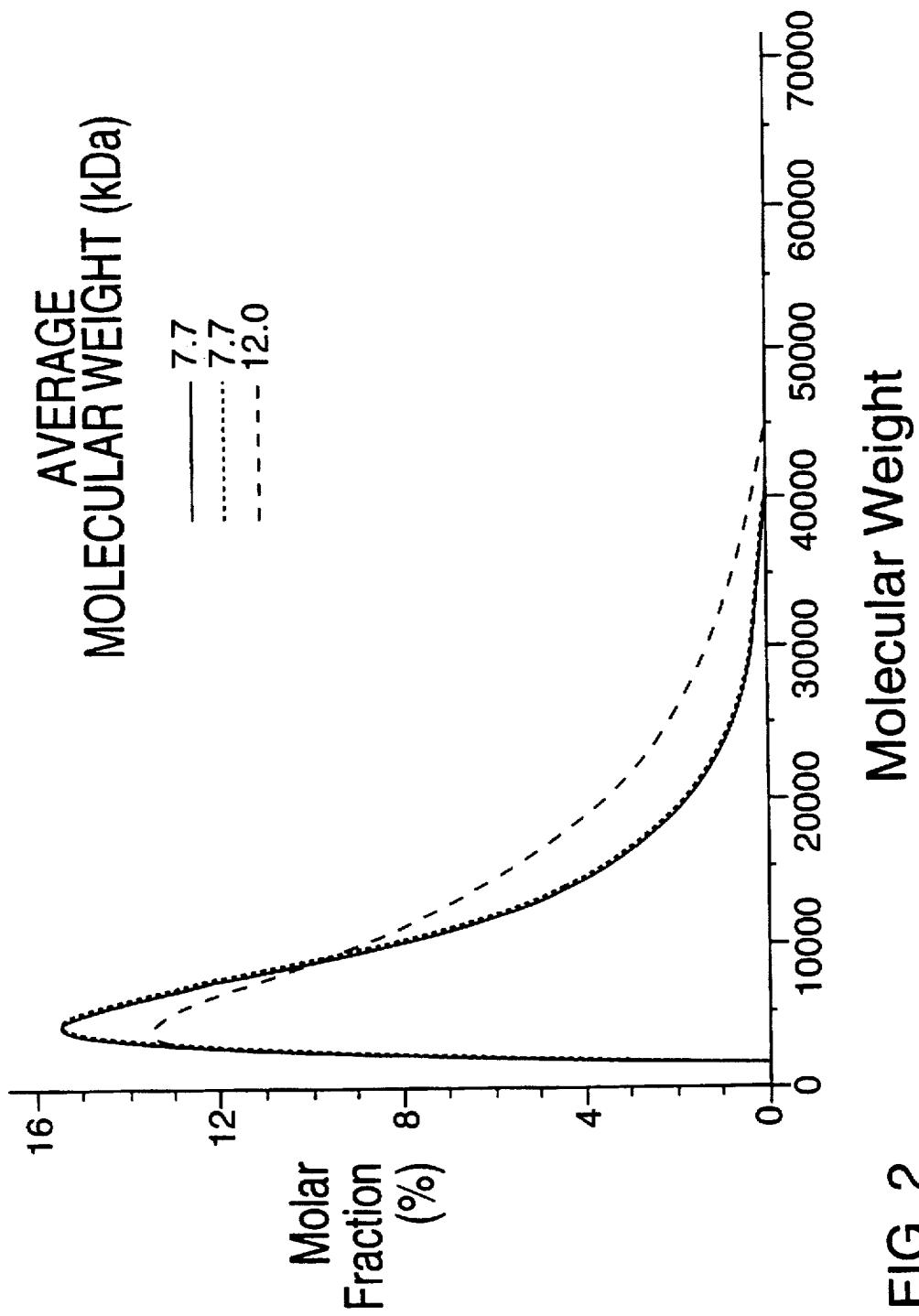
FIG. 1

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COPOLYMER-1 IMPROVEMENTS IN COMPOSITIONS OF COPOLYMERS

This application is a continuation-in-part of U.S. Ser. No. 08/344,248, filed Nov. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 08/248,037, filed May 24, 1994, now abandoned.

BACKGROUND OF THE INVENTION

Copolymer-1 is a synthetic polypeptide analog of myelin basic protein (MBP), which is a natural component of the myelin sheath. It has been suggested as a potential therapeutic agent for multiple sclerosis (Eur. J. Immunol. [1971] 1:242; and J. Neurol. Sci. [1977] 31:433). All references cited herein are hereby incorporated by reference in their entirety. Interest in copolymer-1 as an immunotherapy for multiple sclerosis stems from observations first made in the 1950's that myelin components such as MBP prevent or arrest experimental autoimmune encephalomyelitis (EAE). EAE is a disease resembling multiple sclerosis that can be induced in susceptible animals.

Copolymer-1 was developed by Drs. Sela, Arnon, and their co-workers at the Weizmann Institute (Rehovot, Israel). It was shown to suppress EAE (Eur. J. Immunol. [1971] 1:242; U.S. Pat. No. 3,849,550). More recently, copolymer-1 was shown to be beneficial for patients with the exacerbating-remitting form of multiple sclerosis (N. Engl. J. Med. [1987] 317:408). Patients treated with daily injections of copolymer-1 had fewer exacerbations and smaller increases in their disability status than the control patients.

Copolymer-1 is a mixture of polypeptides composed of alanine, glutamic acid, lysine, and tyrosine in a molar ratio of approximately 6:2:5:1, respectively. It is synthesized by chemically polymerizing the four amino acids forming products with average molecular weights of 23,000 daltons (U.S. Pat. No. 3,849,550).

It is an object of the present invention to provide an improved composition of copolymer-1.

SUMMARY OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa).

The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

Moreover, the invention relates to a pharmaceutical composition and a method for the treatment of multiple sclerosis, using the above-discussed copolymer-1.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 displays the molecular weight distribution of three batches of copolymer-1, showing the proportion of species with molecular weight above 40 KDa. FIG. 2 shows similar data relating to the molar fraction.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a composition of copolymer-1 substantially free of species of copolymer-1 having a molecular weight of over 40 kilodaltons (KDa). Preferably, the composition contains less than 5% of species

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of copolymer-1 having a molecular weight of 40 KDa or more. More preferably, the composition contains less than 2.5% of species of copolymer-1 having a molecular weight of 40 KDa, or more.

5 The invention further relates to a copolymer-1 having over 75% of its molar fraction within the molecular weight range from about 2 KDa to about 20 KDa.

In addition, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8.6 KDa.

10 In particular, the invention relates to a copolymer-1 having an average molecular weight of about 4 to about 8 KDa and a copolymer-1 having an average molecular weight of about 6.25 to about 8.4 KDa.

15 Copolymer-1, according to the present invention, may be prepared by methods known in the art, for example, the process disclosed in U.S. Pat. No. 3,849,550, wherein the N-carboxyanhydrides of tyrosine, alanine, γ -benzyl glutamate and E-N-trifluoro-acetyllysine are polymerised at ambient temperature in anhydrous dioxane with diethylamine as initiator. The deblocking of the γ -carboxyl group of the glutamic acid is effected by hydrogen bromide in glacial acetic acid and is followed by the removal of the trifluoroacetyl groups from the lysine residues by 1M piperidine. For the purposes of the application, the terms

20 "ambient temperature" and "room temperature" should be understood to mean a temperature ranging from about 20° to about 26° C.

25 The copolymer-1 with the required molecular weight profile can be obtained either by methods known per se. Such methods include chromatography of copolymer-1 containing high molecular weight species and collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight

30 species with subsequent purification by dialysis or ultrafiltration. A further method to obtain copolymer-1 with the desired molecular weight profile is by preparing the desired species while the amino acids are still protected and then obtain the correct species directly upon removing the protection.

35 The compositions of the present invention may be formulated by conventional methods known in the art. Preferably, the composition is lyophilized and formed into an aqueous solution suitable for sub-cutaneous injection. Alternatively, copolymer-1 may be formulated in any of the 40 forms known in the art for preparing oral, nasal, buccal, or rectal formulations of peptide drugs.

45 Typically, copolymer-1 is administered daily to patients suffering from multiple sclerosis at a dosage of 20 mg.

50 The invention will be exemplified but not necessarily limited by the following Examples.

EXAMPLE 1

Chromatographic method of preparation of low-toxicity copolymer-1 Two batches of copolymer-1 were prepared 55 according to the methods known in the art, for example, U.S. Pat. No. 3,849,550.

One batch was then subjected to chromatographic separation, as described below.

A column for gel filtration, FRACTOGEL TSK HW55 60 (600×26 mm) was prepared in a Performance 26 Merck cartridge according to the manufacturer's instructions. The column was equilibrated with water and acetone solution was injected for total volume determination. The column was equilibrated with 0.2M ammonium acetate buffer pH 5.0. 30 ml copolymer-1 samples (20 mg/ml, in 0.2M ammonium acetate pH 5.0) were loaded on the column and fractions were collected every 10 minutes. A fraction having

an average molecular weight of 7–8 KDa was isolated between 120–130 minutes (Batch A).

Molecular Weight Analysis

UV absorbance at 275 nm was determined in a UVIKON 810 spectrophotometer. Samples were diluted to obtain a UV absorbance lower than 1 Absorption Unit. The molecular distribution of the 2 batches was determined on a calibrated gel filtration column (Superose 12).

Copolymer-1 batch A was found to have an average molecular weight of 7–8 KDa. 2.5% of this batch had a molecular weight above 32 KDa, but no copolymer-1 species present in this batch had a molecular weight of over 40 KDa.

The other batch of copolymer-1 which was not subjected to chromatography, had an average molecular weight of 12 KDa. 2.5% of the batch had a molecular weight above 42 KDa and 5% of the total copolymer-1 species in this batch had a molecular weight of over 40 KDa.

EXAMPLE 2

Toxicity Analysis

A: In Vivo

Three batches of copolymer-1 having an average molecular weight of 7.3 and 8.4 KDa (less than 2.5% copolymer-1 species over 40 KDa) and 22 KDa (more than 5% copolymer-1 species over 40 KDa) were subjected to the toxicity test described below. In each case 5 mice were used in each experimental group.

Method

Copolymer-1 was dissolved in distilled water to yield a solution of 2 mg/ml of the active ingredient. Each mouse was injected with 0.5 ml of the test solution into the lateral tail vein. Mice were observed for mortality and relevant clinical signs over a 48 hour period. Observations were recorded 10 minutes, 24 hours and 48 hours post-injection. If, at the end of 48 hours, all the animals were alive and no adverse signs had been observed, then the batch was designated "non-toxic". If, however, one or more of the mice had died or had shown adverse signs, then the batch was designated "toxic".

The batches with the average molecular weight of 7.3 and 8.4 KDa were both designated "non-toxic", whereas in the batch with the average molecular weight of 22 KDa, 3 out of 5 mice had died at the end of 48 hours, and it was consequently designated "toxic".

B: In Vitro

RBL—Degranulation test

I. Introduction

Histamine (or serotonin) release from basophile is an in vitro model for immediate hypersensitivity. The Rat Basophilic Leukemia cell line (RBL-2H₃) was developed and characterized as a highly sensitive, uniform, easy to maintain in culture and reproducible system (E. L. Basumian, C. Isersky, M. G. Petrino and R. P. Siraganian. *Eur. J. Immunol.* 11, 317 (1981)). The physiological stimulus for histamine release involves binding of the antigen to membrane-bound IgE molecules, resulting in the latter's cross-linking and the consequent triggering of an intricate biochemical cascade. Beside these physiological, immunoglobulin-mediated triggers, degranulation can be induced by different non-IgE-mediated stimuli. Among these are various peptides and synthetic polymers, e.g. polylysine (R. P. Siraganian. *Trends in Pharmacological Sciences*, October 432 (1983)). The RBL degranulation test is, therefore, used in order to screen out those batches of copolymer-1 which evoke substantial degranulation and thus might elicit undesirable local and/or systemic side effects.

II. Principle of the test method

Rat Basophilic Leukemia cells (RBL-2H₃), are loaded with [³H]-serotonin, followed by incubation with 100 µg of the copolymer-1 to be tested. Batches of copolymer-1 which induce non-specific degranulation, release [³H]-serotonin into the medium. The radioactivity in the medium is counted by a scintillation counter and the total radiolabeled serotonin incorporated into the cells is determined in the pelleted cells. Percent degranulation is calculated as the percentage of serotonin released out of the total incorporated.

III. Results

Four batches of copolymer-1, with average molecular weight between 6,250–14,500 were analyzed for both % of the species with molecular weight over 40 KDa and for degranulation of RBL's. Results are summarized in the following table.

	Average M.W. (Daltons)	% of species with M.W. over 40 KDa	% Serotonin Release
20	6,250	<2.5	12.4
	7,300	<2.5	21.0
	13,000	>5	66.9
	14,500	>5	67.8

As can be seen, when the % of high molecular weight species is low (<2.5), the % release of serotonin, indicative of toxicity, is low, and vice versa.

EXAMPLE 3

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. *Eur. J. Immun.* Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), γ -benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried. The removal of the gamma-benzyl blocking groups from the glutamate residue is carried out by treating the protected copolymer-1 with 33% hydrobromic acid in glacial acetic acid at room temperature for 6–12 hours with stirring. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

EXAMPLE 4

Preparation of Trifluoroacetyl-Copolymer-1

Protected copolymer-1 is prepared as described by Teitelbaum et al. *Eur. J. Immun.* Vol. 1 p. 242 (1971) from the N-carboxyanhydrides of tyrosine (18 g), alanine (50 g), τ -benzyl glutamate (35 g) and trifluoroacetyllysine (83 g) dissolved in 3.5 liters of dioxane.

The polymerization process is initiated by the addition of 0.01–0.02% diethylamine. The reaction mixture is stirred at room temperature for 24 hours and then poured into 10 liters water. The product (protected copolymer-1) is filtered, washed with water and dried.

Protected copolymer-1 is treated with 33% HBr in acetic acid which removes the omega benzyl protecting group from the 5-carboxylate of the glutamate residue and cleaves the polymer to smaller polypeptides. The time needed for obtaining copolymer-1 of molecular weight 7,000±2,000 Da depends on the reaction temperature and the size of protected copolymer-1. At temperatures of between 20°–28° C. a test reaction is performed on every batch at different time periods for example, from 10–50 hours.

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The results concerning the molecular weights of these small scale reactions are calculated and a curve of molecular weight against time is drawn. The time needed for obtaining molecular weight $7,000 \pm 2,000$ Da is calculated from the curve and performed on larger scale reaction. On average, working at 26° C. the time period is 17 hours. The product is poured into excess water, filtered, washed and dried, yielding the trifluoroacetyl-copolymer-1.

Preparation of low-toxicity copolymer-1

20 g of trifluoroacetyl-copolymer-1 are dispersed in 1 liter of water to which 100 g piperidine are added. The mixture is stirred for 24 hours at room temperature and filtered. The solution of crude copolymer-1 is distributed into dialysis bags and dialyzed at 10°–20° C. against water until a pH=8

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is attained. It is then dialyzed against about 0.3% acetic acid and again water until a pH=5.5–6.0 is obtained. This solution is then concentrated and lyophilized to dryness.

What is claimed is:

5 1. A method of manufacturing copolymer-1, comprising reacting protected copolymer-1 with hydrobromic acid to form trifluoroacetyl copolymer-1, treating said trifluoroacetyl copolymer-1 with aqueous piperidine solution to form copolymer-1, and purifying said copolymer-1, to result in copolymer-1 having a molecular weight of about 5 to 9 kilodaltons.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : **5,800,808**

DATED : **September 1, 1998**

Page 1 of 2

INVENTOR(S) : **Konfino, et al**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Page 1, right column, line 1, change "onExperimen-" to --on
Experimen--

Page 1, right column, line 23, change "Automimmunity" to
--Autoimmunity--;

Page 2, left column, line 27, change "1983, pp." to --1983, 42, pp.--;

Page 2, left column, line 14 from bottom, change "1985," to
--1985, 35,--;

Page 2, right column, lines 8 and 9, change "The....Sclerosis" to
--"The....Sclerosis"--;

Page 2, right column, lines 17 and 18, change "Copolymer 1...(letter)"
to
--"Copolymer 1... (letter)"--;

Column 1, line 8, change "1994, pp." to --1994, 1, pp.--;

Column 1, line 34, change "Marland" to --Maryland--;

Column 1, lines 35 and 36, delete "Tel-Aviv University, University of
Marland School of Medicine,";

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : **5,800,808**

DATED : **September 1, 1998**

Page 2 of 2

INVENTOR(S) : **Konfino, et al**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 17, change "y-benzyl to --y-benzyl--;
Column 2, line 20, change "y-benzyl to --y-benzyl--;
Column 4, line 33, change "y-benzyl to --y-benzyl--;
Column 4, line 52, change "r-benzyl to --y-benzyl--;
Column 4, line 60, change "omega" to --gamma--;

Signed and Sealed this
Third Day of April, 2001

Attest:



NICHOLAS P. GODICI

Attesting Officer

Acting Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,800,808
APPLICATION NO. : 08/447146
DATED : September 1, 1998
INVENTOR(S) : Konfino et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the face of the patent, # (73) Assignee, change "Veda" to --Yeda--.

Signed and Sealed this

Twenty-second Day of May, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office